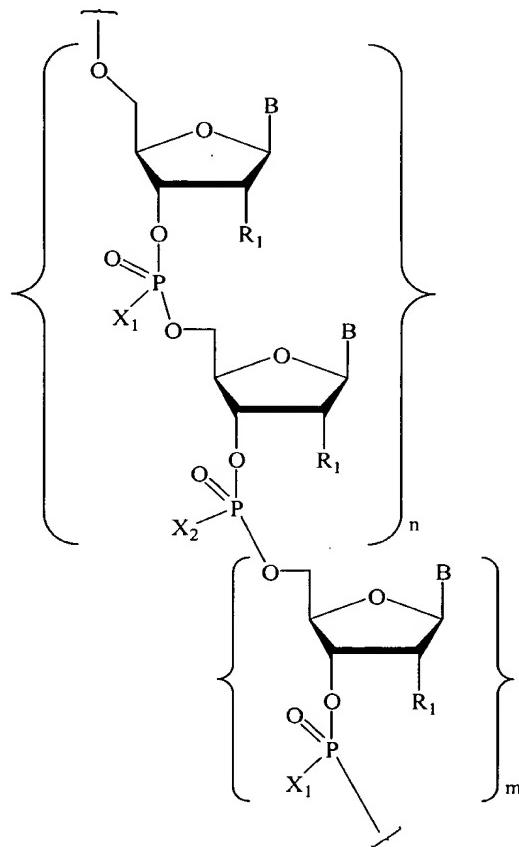


This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

Claims 1-27 (canceled).

Claim 28 (previously amended): A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:



wherein:

- each B is a nucleobase;
- one of X₁ or X₂ is O, and the other of X₁ or X₂ is S;
- each R₁, is, independently, H, hydroxyl, C₁-C₂₀ alkyl, C₃-C₂₀ alkenyl, C₂-C₂₀ alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-

alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula $Z-R_{22}-(R_{23})_v$;

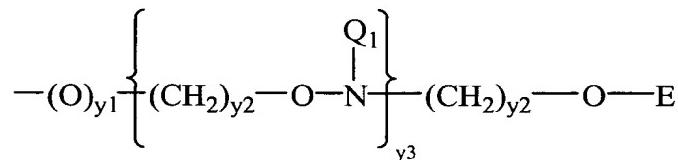
Z is O, S, NH, or $N-R_{22}-(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

v is from 0 to about 10;

or R_1 has the formula:



wherein:

y_1 is 0 or 1;

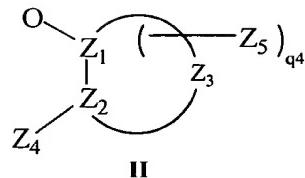
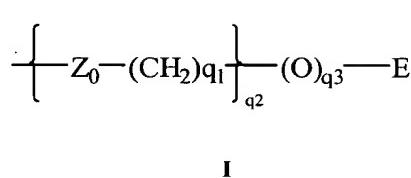
y_2 is independently 0 to 10;

y_3 is 1 to 10;

E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2 , together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1 , SM_1 , or $\text{N}(\text{M}_1)_2$;

each M_1 is, independently, H, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C(=NH)N(H)M₂, C(=O)N(H)M₂ or OC(=O)N(H)M₂;

M_2 is H or C₁-C₈ alkyl;

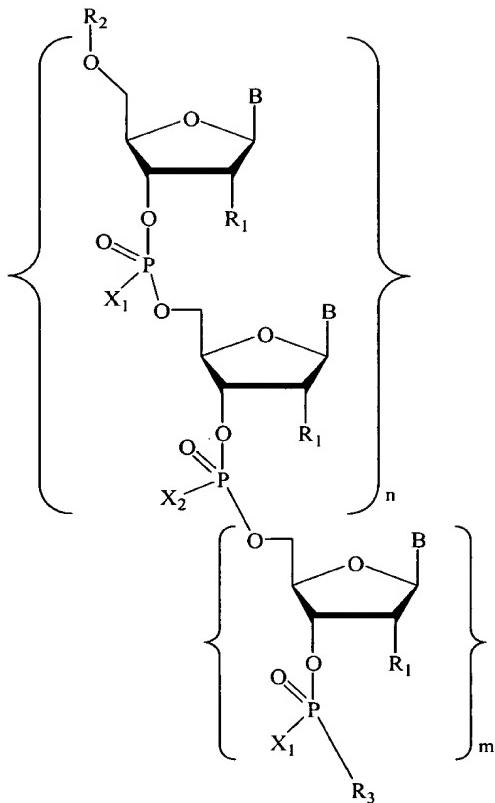
Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(Q₁)(Q₂), OQ₁, halo, SQ₁ or CN;

n is from 2 to 50; and

m is 0 or 1.

Claim 29 (previously amended): A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:



wherein:

each B is a nucleobase;

X₁ is S;

X₂ is O;

each R₁ is, independently, H, hydroxyl, C₁-C₂₀ alkyl, C₃-C₂₀ alkenyl, C₂-C₂₀ alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R₁ is a group of formula Z-R₂₂-(R₂₃)_v;

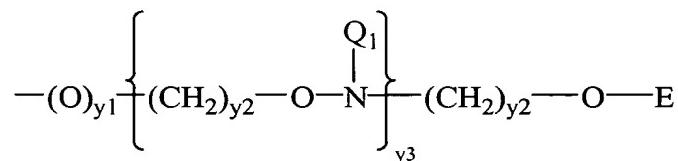
Z is O, S, NH, or N-R₂₂-(R₂₃)_v;

R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

v is from 0 to about 10;

or R_1 has the formula:



$y1$ is 0 or 1;

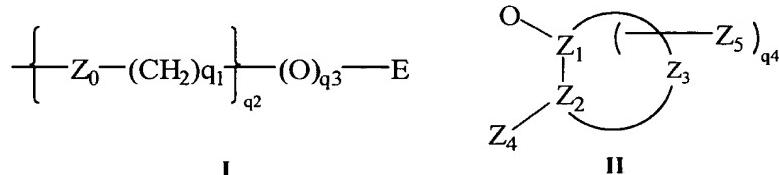
$y2$ is independently 0 to 10;

$y3$ is 1 to 10;

E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2 , together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;
 q^4 is, 0, 1 or 2;
 Z_4 is OM_1 , SM_1 , or $N(M_1)_2$;
each M_1 is, independently, H, C₁-C₈ alkyl, C₁-C₈ haloalkyl,
 $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;
 M_2 is H or C₁-C₈ alkyl;

Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1 , halo, SQ_1 or CN ;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide; and

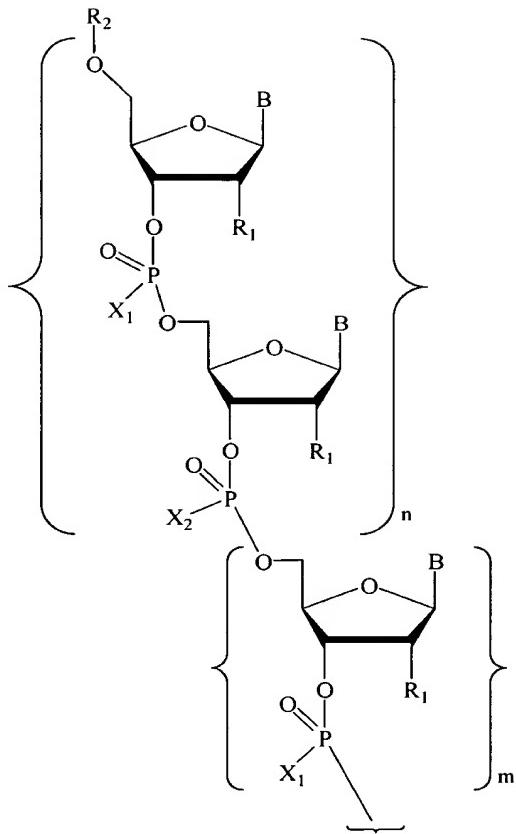
R_3 is OH, an oligonucleotide, or a linker connected to a solid support.

Claim 30 (previously amended): A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:

(5') $W^1-W^2-W^3$ (3')

wherein:

W^1 has the Formula:



wherein:

each B is a nucleobase;

one of X_1 or X_2 is O, and the other of X_1 or X_2 is S;

each R_1 is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula $Z-R_{22}-(R_{23})_v$;

Z is O, S, NH, or $N-R_{22}-(R_{23})_v$;

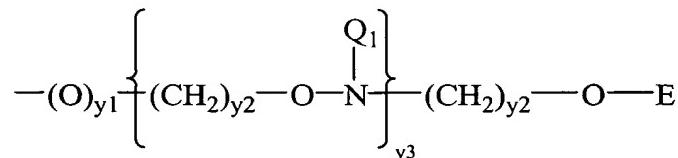
R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-

aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

v is from 0 to about 10;

or R₁ has the formula:



y1 is 0 or 1;

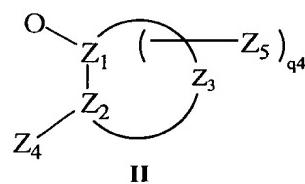
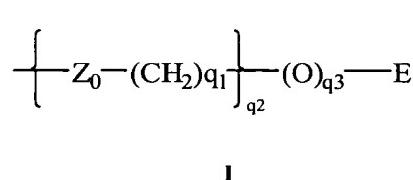
y2 is independently 0 to 10;

y3 is 1 to 10;

E is C₁-C₁₀ alkyl, N(Q₁)(Q₂) or N=C(Q₁)(Q₂);

each Q₁ and Q₂ is, independently, H, C₁-C₁₀ alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q₁ and Q₂, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R₁ has one of formula I or II:



wherein:

Z₀ is O, S, or NH;

q¹ is from 0 to 10;

q² is from 1 to 10;

q³ is 0 or 1;

q⁴ is 0, 1 or 2;

Z_4 is OM_1 , SM_1 , or $N(M_1)_2$;

each M_1 is, independently, H, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C(=NH)N(H)M₂, C(=O)N(H)M₂ or OC(=O)N(H)M₂;

M_2 is H or C₁-C₈ alkyl;

Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

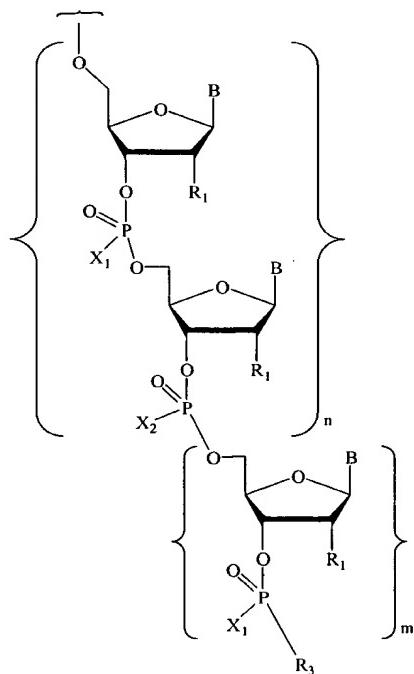
Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(Q₁)(Q₂), OQ₁, halo, SQ₁ or CN;

n is from 2 to 50; and

m is 0 or 1;

R₂ is H, a hydroxyl protecting group, or an oligonucleotide;

W³ has the Formula:



wherein R₃ is OH, an oligonucleotide, or a linker connected to a solid support; and

DOCKET NO.: ISIS-4847
Application No.: 09/965,551
Office Action Dated: April 24, 2003

PATENT

W^2 is a plurality of covalently bound nucleosides linked by phosphodiester or phosphorothioate linkages.

Claims 31-51 (canceled).

Claim 52 (Reinstated – formerly claim no. 34): The method of claim 28 wherein R_1 is -O-CH₂-CH₂-O-CH₃.

Claim 53 (Reinstated – formerly claim no. 35): The method of claim 28 wherein n is about 5 to about 50.

Claim 54 (Reinstated – formerly claim no. 36): The method of claim 28 wherein n is about 8 to about 30.

Claim 55 (Reinstated – formerly claim no. 37): The method of claim 28 wherein n is about 4 to about 15.

Claim 56 (Reinstated – formerly claim no. 38): The method of claim 28 wherein n is 2 to about 10.

DOCKET NO.: ISIS-4847
Application No.: 09/965,551
Office Action Dated: April 24, 2003

PATENT

Claim 57 (Reinstated – formerly claim no. 39): The method of claim 29 wherein R₁ is -O-CH₂-CH₂-O-CH₃.

Claim 58 (Reinstated – formerly claim no. 40): The method of claim 29 wherein R₂ is H, and R₃ is OH.

Claim 59 (Reinstated – formerly claim no. 41): The method of claim 29 wherein R₂ is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

Claim 60 (Reinstated – formerly claim no. 42): The method of claim 29 wherein R₃ is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

Claim 61 (Reinstated – formerly claim no. 43): The method of claim 29 R₂ and R₃ are each a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

Claim 62 (Reinstated – formerly claim no. 44): The method of claim 30 wherein R₁ is -O-CH₂-CH₂-O-CH₃.

Claim 63 (Reinstated – formerly claim no. 45): The method of claim 30 wherein R₂ is H, and R₃ is OH.

Claim 64 (Reinstated – formerly claim no. 46): The method of claim 30 wherein n is about 5 to about 50.

Claim 65 (Reinstated – formerly claim no. 47): The method of claim 30 wherein n is about 8 to about 30.

Claim 66 (Reinstated – formerly claim no. 48): The method of claim 30 wherein n is about 4 to about 15.

Claim 67 (Reinstated – formerly claim no. 49): The method of claim 30 wherein n is 2 to about 10.

Claim 68 (Reinstated – formerly claim no. 50): The method of claim 30 wherein W² is a plurality of covalently bound nucleosides linked by phosphodiester linkages.

Claim 69 (Reinstated – formerly claim no. 51): The method of claim 30 wherein W² is a plurality of covalently bound nucleosides linked by phosphorothioate linkages.--